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Unpicking observational relationships between hip shape and osteoarthritis: hype or hope?

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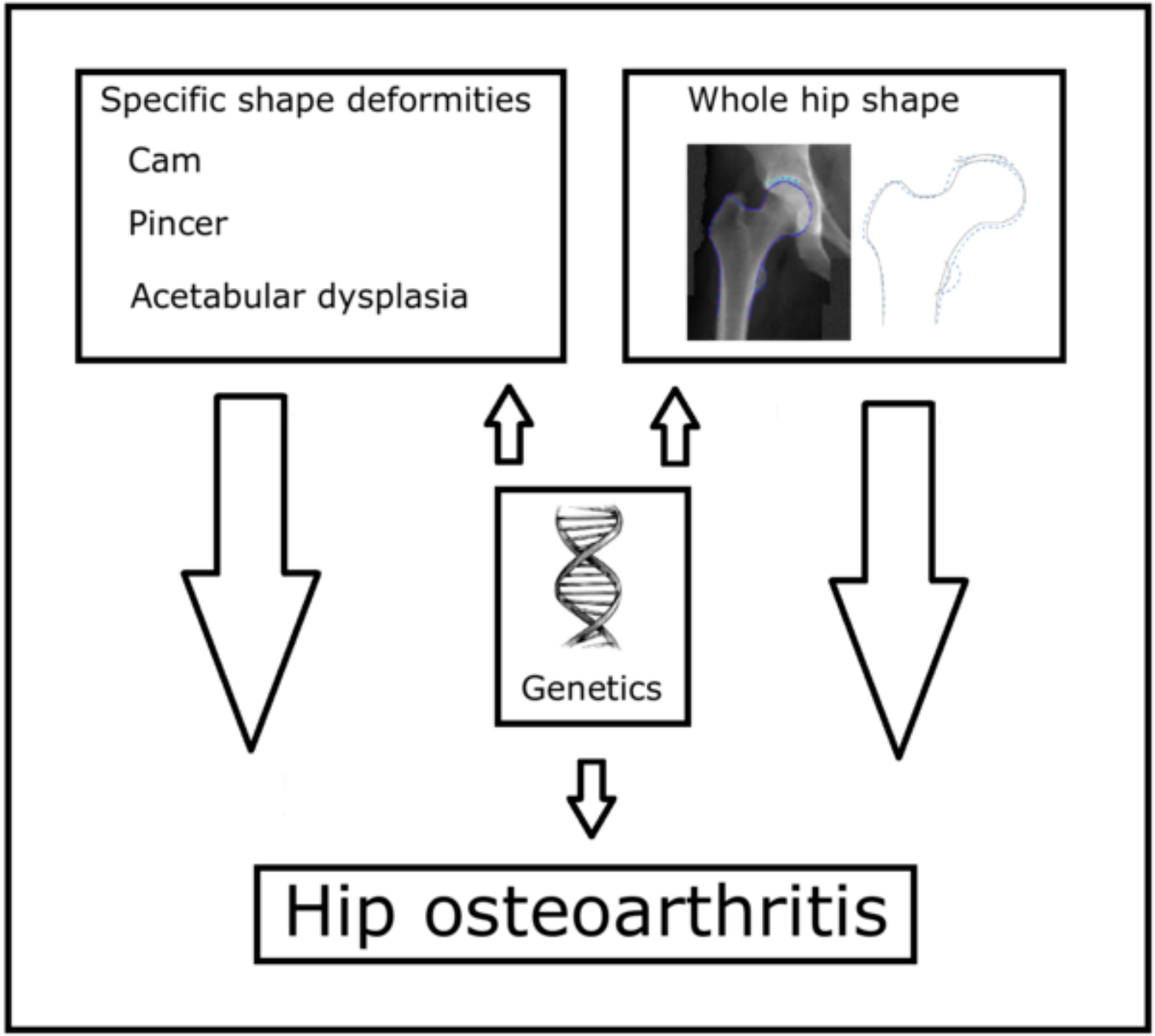
Figure 1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Unpicking observational relationships between hip shape and osteoarthritis: hype or hope?

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Purpose of review

To review recent findings concerning the observational relationship between hip shape and hip osteoarthritis (HOA) and their shared genetic influences, and the potential for clinical application.

Recent findings

Recent observational studies have strengthened the evidence that specific shape deformities, such as cam and acetabular dysplasia, are related to HOA. Statistical shape modelling has emerged as a method to measure hip shape holistically, with the added advantage that this can be applied to DXA scan images. This has led to several additional aspects of hip shape variation being identified, such as a wider femoral neck and larger lesser trochanter, in association with HOA. Furthermore, this method has formed the basis of genetic studies identifying novel genetic influences on hip shape, several of which are shared with known genetic risk factors for HOA.

Summary

Shared genetic influences of hip shape and HOA raise the possibility that hip shape plays a casual role in the development of HOA, justifying preventative approaches aiming to combat these adverse consequences.

Key words: Osteoarthritis, hip shape, genetics

Introduction

Osteoarthritis (OA) affects 250 million individuals worldwide, and the number is steadily rising as the population ages (1-3). OA is characterised by cartilage loss, joint space narrowing, bone formation, inflammation, pain and loss of function of the joint (4). Hip OA (HOA) is the third most commonly affected joint, after knees and hands, with prevalence ranging from 2-43% depending on the population and how it is defined (3). Though effective interventions to prevent onset and delay progression are currently lacking, it may be possible to develop these in future, based on greater understanding of the risk factors involved.

As previously reviewed by Baker-LePain and Lane, hip shape appears to be an important risk factor for HOA with subtle changes in hip morphology present in up to 90% of cases with primary HOA (5), possibly reflecting shared genetic influences (6). Here we aim to provide a more up to date perspective on the relationship between hip shape and HOA, in light of methodological advances such as DXA-derived hip shape, and recent large-scale genome wide association studies (GWAS) for HOA and hip shape. (Fig1)

Hip shape and its observational relationship with osteoarthritis

HOA is a complex and phenotypically heterogeneous disease (7). In this review we focus on epidemiological studies of HOA defined as radiographic (based on scoring criteria such as Kellgren-Lawrence (8) or Croft (9)), symptomatic (assessed by questionnaire (10) and/or examination (11)) or total hip replacement (THR) (12). As previously reported, the correlation between radiographic HOA (RHOA) and symptomatic HOA (SHOA) is known to be inconsistent (6, 13). Our review focuses on hip shape derived from two dimensional (2D) imaging; although computed tomography and magnetic resonance imaging have both been used for

three dimensional (3D) shape modelling (14, 15), they have yet to feature in large scale epidemiological studies described here.

Specific hip shape deformities

Since the Baker-LePain et al review (6), many large epidemiological studies have investigated the relationship between hip shape and OA, as summarised in Table 1. The most recent studies focus on subtler variations in hip shape, in contrast to severe congenital dysplasias such as developmental dysplasia of the hip (DDH) which has well established links with early onset HOA(16-18).

Femoro-acetabular impingement (FAI) is a symptomatic condition characteristic of cam, pincer or mixed (the presence of both) deformity (19), which is thought to increase the risk of developing HOA(20). Cam deformity represents a bulging of the lateral femoral head resulting in a non-spherical head and is most commonly defined by measuring alpha angles on anterior-posterior or lateral radiographs(21). It is thought to develop during adolescence, in particular as a result of high impact activities (21, 22). Previous studies reported associations between cam deformity (defined by alpha angle) and worsening RHOA (23), incident RHOA(24), and end-stage HOA (defined as either incident RHOA or THR) (25, 26) with odds ratios (OR) ranging from 1.05-9.66 (24, 25). For example, the largest study (n=4,438) observed an OR 2.11 for incident RHOA or THR(26). The triangular index is a further measure of cam deformity and has been linked with prevalent RHOA(27) and incident end-stage HOA(28).

Another component of FAI, pincer deformity, representing over-coverage of the acetabulum relative to the femoral head, has also been suggested to be a risk factor for HOA (20, 29).

Consistent with this suggestion, using a CEA cut off of ≥45degrees, Gosvig et al reported an association with prevalent RHOA (RR 2.4 [2.0-2.9]) (27). On the other hand, in the CHECK and Chingford cohorts, pincer deformity, defined as a centre-edge angle (CEA) >40 degrees, was not associated with an increased risk of incident RHOA or THR (30, 31),

Acetabular dysplasia describes a lack of acetabular coverage of the femoral head, measured with a CEA on pelvic radiographs (range <20-28 degrees) (24-26) and is distinct from FAI. Recent studies have shown a relationship of acetabular dysplasia with incident RHOA and THR, replicating earlier studies and suggesting it represents a further hip joint deformity contributing to the pathogenesis of HOA (24, 26).

Global assessment of proximal femur/ hip shape

Statistical shape modelling (SSM) has been developed to describe joint shape as a whole, using principal component analysis to generate hip shape modes (HSMs) describing variation in hip shape in a given data set (typically a subset of HSMs, which explain between 85-95% of variation in hip shape are used in analysis (11, 12, 32)). These HSMs encompass different areas of the joint such as the acetabulum, femoral head and femoral shaft in one measurement. This enables relationships between hip shape and disease outcomes to be examined in a hypothesis-free manner, offering the potential to identify novel aspects of hip shape contributing to HOA. Gregory et al first applied this technique to hip radiographs to investigate the relationship with hip fracture (33) before looking at RHOA(34).

In two recent prospective cohorts (CHECK and Chingford), where SSM was applied to hip radiographs, six HSMs predicted THR but only one HSM (describing a flatter femoral neck to head junction, flatter greater trochanter and prominent acetabular wall) was predictive in

both cohorts (35). In the Johnston County OA project, three HSMs were associated with incident symptomatic radiographic HOA (as a single phenotype); in particular HSM2 representing a cam-type deformity, and larger greater and lesser trochanters [OR 1.47], and HSM3 representing smaller greater trochanter and larger femoral head [OR 1.54] (36). In a separate study, the authors also found that smaller femoral head and lesser trochanter was associated with RHOA in the small sample of African American women (37).

DXA-derived hip shape

Whereas the aforementioned studies are based on radiographs, SSM has subsequently been extended to hip dual X-ray absorptiometry (DXA) scans (38), for which greater numbers of population based cohorts are available. Recently, in the Osteoporotic Fractures in Men Study (MrOS), DXA-derived SSM from 4,100 individuals found five HSMs to be associated with prevalent RHOA [negative SD shapes OR 0.73-0.83 and positive SD shapes OR 1.23-1.24] and of these HSM3 was also associated with hip pain as assessed by pain scores and clinical examination [OR 0.88 and 0.83 respectively] (11). In the Tasmanian Older Adult Cohort (TASOAC), DXA-derived hip shape showed association with incidence and progression of HOA, specifically HSM2 and 4 which predicted THR [OR 1.6 & 0.6 respectively] (39). However, whereas HSM2 was positively related to risk of THR, this was negatively related to RHOA.

In both these DXA studies, as well as representing cam or pincer-type deformities, proximal femur HSMs found to be associated with HOA were also related to a range of other features previously reported to be associated with HOA. These include a larger greater and lesser trochanters seen by Nelson et al in their SSM study based on radiographs (36), and a wider femoral neck associated with HOA when measured geometrically (Castano-Betancourt et al (28) and Javaid et al (40)). A limitation of SSM is that it is difficult to establish which particular

feature of hip shape is relevant to HOA and further work is needed to clarify these relationships. Interestingly, in analysis based on a sub-regional shape model limited to the lesser trochanter, and validated against 3D hip shape from CT, lesser trochanter size showed a similar relationship with prevalent RHOA in MrOS, compared to HSMs derived from the whole proximal femur (Faber et al, manuscript in preparation) (41). The reported associations between HSMs representing a pincer-type deformity and RHOA contrast with null relationships reported in radiographic studies that assessed pincer deformity by measuring CEA (30, 31). It may be that the presence of pincer-type deformity is only important in the presence of other variations in shape such as a larger greater and lesser trochanters as seen in HSM1 in MrOS (11) and HSM2 in TASOAC (39) that are not captured when assessing pincer deformity on its own (30).

When comparing results from different studies it is important to note that HSMs are specific to the population being examined, since they are derived from principle components analysis applied to the specific image set in question. Therefore, results cannot be directly compared between studies. However, one way of overcoming this issue is to build an SSM model on multiple cohorts combined, as done in a recent GWAS meta-analysis of hip shape (42). Alternatively, an existing SSM template can be applied as a reference, as exemplified by our recent study in adolescents where we applied a template built from adult images to enable comparison of hip shape between different ages (43).

Genetic influences on hip shape and OA

To date, GWASs have identified 86 single nucleotide polymorphisms (SNPs) associated with OA at any site (44), defined as radiographic OA, severe OA (defined by joint replacement) or self-reported OA (44-49). Of these, a number of variants associated with HOA specifically, or HOA and OA at other sites, have also been found to associate with measures of hip shape, as shown in Table 2.

The majority of recently published studies exploring genetics of hip shape used measures quantified with SSM. For example, a longitudinal study of Caucasian women reported associations between two *FRZB* SNPs and proximal femur shape, of which rs288326 was associated with HSM2 which predicted incident RHOA (50). The only GWAS meta-analysis of SSM DXA-derived hip shape identified nine novel variants associated with hip shape. Of those, three were found to associate with HOA in previous GWASs based on arcOGEN and UK Biobank (42). Two of these loci (near *PTHLH* and *RUNX1*), which were associated with HSM1, are known regulators of endochondral bone formation, raising the possibility that altered development of hip shape may have implications for future risk of HOA (42). A further locus, *ASTN2,* associated with HSM2 (42) (a RHOA associated shape in MrOS (Faber et al, manuscript in preparation (41))) was also found to associate with HSM5 in a cohort of subjects with unilateral HOA (51). In contrast to SSM derived hip shape, Zengini et al explored genetic associations with geometric measures of hip shape (defining acetabular dysplasia and cam deformity) using data from UK Biobank and the Rotterdam studies, with largely null findings (52).

In studies performed in older adults it is difficult to distinguish shape changes that are the direct result of OA, from those that lead to OA development . For example, rather than pre-dating OA, pincer-type deformities may result from osteophytes formed as part of the OA process (11). Findings of associations between known OA risk loci and hip shape in younger individuals who are likely to be disease free could point towards causal variants for OA development. For example, in a look-up study of known OA susceptibility loci in peri-menopausal women, *PTHLH* rs10492367 SNP (in high linkage disequilibrium, r^2=0.74, with rs10743612 SNP reported in the above GWAS meta-analysis of DXA derived hip shape in adults and previously found to associate with hip shape in adolescents (43)) was associated with a greater height-to-width ratio of upper femur (53), further reinforcing the suggestion that altered femoral morphology plays a role in HOA development. In addition, the *COL11A1* locus was associated with lateral displacement of the femoral head and previous studies reported associations of this locus with hip bone size (54), and altered load-induced cartilage damage in *COL11A1* insufficient mice (55). In addition *COL11A1* mutations are associated with Stickler's syndrome which causes accelerated HOA (53, 56, 57). This look-up study also reported an association between *DOTL1* rs12982744 and superolateral joint space, consistent with previous GWAS findings implicating *DOT1L* with joint space width (46, 52).

DDH, characterized by uncovering of the femoral head and in its most severe forms complete dislocation of the hip joint (58), is a common cause of premature HOA in young adults (59) and has a strong genetic component (60). A recent GWAS identified a robustly replicating association between genetic locus at *GDF5* (previously found to be associated with HOA risk (45, 52)) and DDH case status (47). In addition, *GDF5* has been shown to affect proximal femur

development in animal studies (61) consistent with the suggestion that OA development is mediated through joint shape and variants associated with hip morphology are likely to mediate this relationship.

Clinical utility of hip shape HOA relationships

As discussed above, evidence that certain OA susceptibility loci are associated with hip shape in cohorts thought to be free of HOA suggests that at least some of the hip shape variations identified precede the development of OA, consistent with a causal role. Identification of further genetic influences on hip shape should enable methods such as Mendelian randomisation (MR) to be applied to examine the causal relationship between hip shape and HOA, by providing instrumental variables for hip shape(62). To the extent that hip shape alterations play a causal role in HOA development, this would provide justification for developing novel preventative approaches aiming to combat these adverse consequences. The latter are presumably mediated by adverse biomechanics associated with hip shape, which a number of methods have been developed to model based on finite element analysis (63).

Whereas conservative methods such as physiotherapy and orthotics could be used to combat adverse biomechanical consequences of altered hip shape (64), surgical approaches are also feasible, as exemplified by surgical correction of FAI syndrome, with three recent trials examining physiotherapy versus arthroscopic intervention in this group (65-67). The two largest studies found only a marginal improvement with surgical intervention as compared to physiotherapy (65, 67), with the smallest study showing no difference (66). The follow up periods were short (<2 years) with no evidence that either intervention is protective for HOA.

None of the trials had well defined, objective measures of FAI instead it was at the surgeons discretion reflecting the inconsistent definitions used in epidemiological studies (21). Finally, the physiotherapy interventions varied greatly between these studies, highlighting the uncertainty regarding the best conservative care (64).

Analogous to predictive models for hip fracture risk (68), hip shape measures could also be used to develop HOA prediction tools (69). Variables in such a tool do not need to be causal, merely predictive of the outcome. Using data from CHECK cohort participants, Hosnijeh et al constructed a model to predict incident RHOA. The authors showed that the inclusion of radiographic measures of acetabular dysplasia and cam deformity (defined as the presence of a CEA<20° and an alpha angle of >60°), greatly improved the discriminative ability of their model from AUC 0.60 [95% CI 0.56-0.60] with purely demographic details, to 0.75 [0.72-0.79] (70). It would be useful to examine whether the predictive ability of such tools is further enhanced by including measures of hip shape derived by SSM.

Conclusion

There are strong associations between hip shape and HOA, comprising of a spectrum from severe DDH, to more subtle variation in hip shape such as FAI and those measured by SSM which seem to contribute to HOA risk. However, more work is needed to establish which particular aspects of hip shape and in what combinations, contribute to associations with HOA. Methodological developments in applying SSM to hip DXA scans in large population cohorts have facilitated GWAS of hip shape, which identified novel genetic influences on hip shape. Findings to date have highlighted the role of developmental genes involved in

endochondral bone formation and pointed to an overlap with genetic risk factors for OA. These findings not only point to biological pathways involved in hip shape development but may enable opportunities for examining causal relationships between hip shape and HOA based on the application of MR methods. To the extent that hip shape plays a causal role in the development of HOA this would justify new approaches to prevention based on amelioration of adverse consequences of altered biomechanics.

Key points

- There is strong observational evidence that hip shape is associated with HOA
- DXA scans can be used to identify hip shape variation enabling large-scale GWASs
- There is increasing evidence of shared genetic influences between hip shape and HOA
- Whether there is a causal relationship between hip shape and HOA remains unclear

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Figure 1: Schematic diagram for the known associations between hip shape, genetics and hip osteoarthritis

The whole hip shape box shows two images one representing a DXA scan marked up for SSM (left) and the other is the output from SSM showing a HSM ± 2 stand deviations (original figure)

Table 1 Summary of hip shape and OA relationships published since 2010 (adjusted results where available) – original table

Abbreviations: KL = Kellgren-Lawrence, THR = Total hip replacement, RHOA = radiographic hip osteoarthritis, SHOA = symptomatic hip osteoarthritis, SRHOA = symptomatic radiographic hip osteoarthritis, OR = odds ratio, RR = risk ratio, AP = anteroposterior, LCEA = lateral centre-edge angle, ACEA = anterior centre-edge angle. *Not all papers reported 95% confidence intervals nor p-values. Available statistics listed. **Authors note that statistical significance is not implied from results and therefore not all measures are reported as smaller associations are not adjusted for multiple testing *** At risk OA shape described for HSM **** Only modes significant in both cohorts is featured. Only geometric measures and statistical shape modelling papers included

Study and date	Study size	Measure of hip shape	Definitions of HOA	Findings (effect size [95% CI] p-value)
Continuous geometric measures from X-ray				
Nicholls et al 2011 (31)	135	Alpha angle	THR	OR 1.05 p 0.006
		LCEA	THR	OR 0.89 p 0.004
		Extrusion index	THR	OR 1.06 p 0.005
Castano-Betancourt et al 2013 (28)	688	Wilberg	Incident RHOA (KL) or THR	OR 0.76 [0.63-0.92] p 0.004
		Neck Width	Incident RHOA (KL) or THR	OR 1.60 [1.24-2.05] p 2.45 x 10^{-4}
		Hip axis length	Incident RHOA (KL) or THR	OR 1.49 [1.18-1.90] p 0.001
		Pelvic width	Incident RHOA (KL) or THR	OR 1.43 [1.16-1.75] p 0.001
		Triangular index	Incident RHOA (KL) or THR	OR 1.93 [1.54-2.43] p < 0.0001
Specific hip shape deformities derived from X-ray				
Gosvig et al 2010 (27)	3620	Deep acetabular socket (aka pincer deformity) (CEA≥45°)	Prevalent RHOA (KL)	RR 2.4 [2.0-2.9]
		Pistol grip deformity (aka cam deformity) (triangular index)	Prevalent RHOA (KL)	RR 2.1 [1.7-2.8]
Agricola et al 2013 (30)	720	Acetabular dysplasia (ACEA < 25°)	Incident RHOA (KL)	OR 2.62 [1.44-4.77] p 0.002
			THR	OR 4.34 [1.99-9.47] p 0.000
		Acetabular dysplasia (LCEA < 25°)	Incident RHOA (KL)	OR 2.83 [1.54-5.20] p 0.001
			THR	OR 3.8 [1.84-7.84] p 0.000
	723	Cam deformity (AP Alpha angle>60°)	Incident end-stage OA (KL ≥ 3 or THR)	OR 3.67 [1.68-8.01]

Agricola et al 2013 (25)		Cam deformity (AP Alpha angle>83°)	Incident end-stage OA (KL ≥ 3 or THR)	OR 9.66 [4.72-19.78]
Thomas et al 2014 (24)	358 – RHOA 726 - THR	Cam deformity (AP alpha angle >65°)	Incident RHOA (KL)	OR 1.05 [1.01-1.09] p 0.007
		Acetabular dysplasia (LCEA ≤28°)	Incident RHOA (KL)	OR 0.87 [0.78-0.96] p 0.008
			THR	OR 0.82 [0.75-0.89] p <0.001
		Extrusion index (per SD)	THR	OR 2.50 [1.78-3.49] p<0.001
		Triangular index height (per unit)	Incident RHOA (KL)	OR 1.14 [1.03-1.26] p 0.026
			THR	OR 1.25 [1.10-1.43] p 0.001
Nelson et al 2016** (23)	120	Cam deformity (AP alpha angle >60°)	Incident RHOA (KL>3)	Men OR 3.57 [1.17 – 10.90] Women OR 4.61 [2.09 – 10.16]
Saberi et al 2017 (26)	4,438	Cam deformity (AP alpha angle>60°)	Incident RHOA (KL) or THR	OR 2.11 [1.55-2.87]
		Acetabular dysplasia (LCEA <20°)	Incident RHOA (KL) or THR	OR 2.19 [1.50-3.21]
Statistical shape modelling from X-ray***				
Castano-Betancourt et al 2013 (28)	688	HSM 5 (Less acetabular coverage, wider femoral neck, cam-type bulge, larger lesser trochanter)	Incident RHOA (KL) or THR	OR 0.65 [0.54-0.77] p <0.0001
		HSM 9 (Less acetabular coverage, shorter femoral neck)	Incident RHOA (KL) or THR	OR 1.40 [1.14-1.72] p 0.001
Agricola et al 2013 (12)	723	HSM 7 (Shorter femoral neck, smaller lesser trochanter)	THR	OR 0.54 [0.38-0.78] p 0.001
		HSM 11 (Less acetabular overhang, larger lesser trochanter, less concave femoral head-neck junction)	THR	OR 1.78 [1.28-2.47] p 0.001
		HSM 12 (Greater acetabular overhang, reduced joint space)	THR	OR 2.10 [1.46-3.10] p <0.001

		HSM 15 (Wider femoral neck, flatter femoral head)	THR	OR 1.90 [1.39-2.59] p <0.001
Nelson et al 2014 (36)	342	HSM 2 (Larger femoral head (cam-type bulge), greater trochanter and lesser trochanter)	SRHOA	OR 1.47 [1.03-2.08]
		HSM 3 (Smaller greater trochanter, steeper curve between femoral neck and head)	SRHOA	OR 1.54 [1.09-2.17]
		HSM 11 (not pictured)	SRHOA	OR 1.52 [1.05-2.17]
Agricola et al 2015 **** (35)	664	HSM 17 (flattened femoral head neck junction, flatter greater trochanter, prominent acetabular posterior wall)	THR	OR 0.51 [0.33-0.80] p 0.003 (CHECK cohort) OR 0.41 [0.23-0.82] p 0.01 (Chingford cohort)
Statistical shape modelling from DXA scans***				
Waarsing et al 2010 ***(38)	222	HSM 6 (deep placement of femoral head in acetabulum, pronounced curvature of superior neck)	SHOA (WOMAC)	p 0.0007
		HSM 11 (pronounced curvature of superior neck)	RHOA (KL)	p 0.0015
Ahedi et al 2016 (39)	831	HSM2 (marked acetabular overhang, larger femoral head, greater and lesser trochanter)	Prevalent RHOA (OARSI grading)	OR 0.85 [0.76-95]
		HSM 2 (Less acetabular coverage, smaller trochanters)	THR	OR 1.6 [1.20-2.15]
		HSM 4 (cam-type bulge and larger lesser trochanter)	THR	OR 0.63 [0.50-0.84]
		HSM 6 (greater acetabular overhang and smaller greater trochanter)	RHOA	OR 1.31 [1.01-1.27]
Faber et al 2017 (11)	4,100	HSM 1 (pincer-type deformity, larger femoral head, greater and lesser trochanters)	Prevalent RHOA (Croft score)	OR 1.23 [1.09-1.39] p 8.2×10^{-4}

		HSM 3 (cam-type deformity and larger lesser trochanter)	Prevalent RHOA (Croft score)	OR 0.73 [0.65-0.85] p 4.0 x 10^{-7}
			Prevalent hip pain on walking, examination & WOMAC	OR 0.88 [0.81-0.95], 0.84 [0.76-0.92], 0.87 [0.80-0.93] respectively p <0.005
		HSM 4 (cam-type deformity and lateral displacement of femoral head)	Prevalent RHOA (Croft score)	OR 0.83 [0.73-0.93] p 0.0021
		HSM 8 (pincer-type deformity)	Prevalent RHOA (Croft score)	OR 0.78 [0.69-0.88] p 7.4x10^{-5}
		HSM 10 (cam-type deformity)	Prevalent RHOA (Croft score)	1.24 [1.1-1.41] p 6.1 x 10^{-4}

Table 2. SNP associations with HOA and various measures of hip shape – original table

* OA risk allele shape described; **proxy SNP Abbreviations: HSM = Hip Shape Mode, FN = femoral neck, DDH = developmental dysplasia of the hip, JSN = joint space narrowing, RHOA = Radiographic hip OA

			Association with hip shape			Association with HOA		
Lead SNP	**Gene/locus**	**EA**	**Study population**	**Measure of hip shape***	**Effect size (p value)**	**Study population**	**Effect size (p value)**	**Ref**
rs10743612	*KLHL42/PTHLH*	A	GWAS meta-analysis N = 15,934	HSM1 (proximal femur and acetabulum SSM - flatted femoral head, narrower and longer FN)	beta 0.093 (2.91×10^{-12})	Results looked up in arcOGEN GWAS	OR **1.14 ($9.6x\ 10^{-5}$)	(42, 44)
rs73197346	*RUNX1*	C		HSM1 (proximal femur and acetabulum SSM - curved femoral head, wider and shorter FN)	beta –0.11 (2.52×10^{-10})	Results looked up in UK Biobank GWAS	OR 0.87 (0.006)	
rs1885245	*ASTN2*	G		HSM2 (proximal femur and acetabulum SSM - narrower FN, smaller femoral head and less acetabular coverage)	beta 0.071 (4.95×10^{-9})	Results looked up in arcOGEN GWAS	OR **1.09 (0.003)	
rs10492367	*KLHDC5/PTHLH*	T	3,111 ALSPAC mothers	SSM measured proximal femur and acetabulum shape - (greater height-to-width ratio of upper femur)	Canonical correlation 0.11 (0.000014)	7,410 arcOGEN OA cases and 11,009 controls	OR 1.14 (1.48×10^{-8})	(45, 53)

rs4907986	*COL11A1*	C		Subregional SSM of superior femoral head and acetabulum (superior JSN)	Canonical correlation 0.078 (0.00049)	GWAS meta-analysis 4,349 patients with hip OA and 17,836 European controls	OR 0.89 (1.29×10^{-5})	(53, 71)
rs12982744	*DOT1L*	G		Subregional SSM of superior femoral head and acetabulum (superior JSN)	Canonical correlation 0.077 (0.0024)	GWAS meta-analysis of 11,277 radiographic and symptomatic HOA cases and 67,473 European controls	OR 0.91 (8.1 × 10−8)	(53, 71)
rs4836732	*ASTN2*	T	929 subjects with unilateral hip OA	HSM 5 (based on female proximal femur SSM, superior femoral head size)	(0.0016)	arcOGEN Consortium and arcOGEN Collaborators	(6.11×10^{-10})	(45, 51)
rs6976	*GLT8D1*	T		HSM 7 (based on mixed-sex proximal femur SSM, medial femoral head size)	(0.0003)	arcOGEN Consortium and arcOGEN Collaborators	(7.24×10^{-11})	
rs5009270	*IFRD1*	A		combination of HSM 3, 4, and 9 of the mixed-sex proximal femur SSM	(0.0004)	11,277 cases of radiographic and symptomatic hip OA and 67,473 controls	OR 1.10 (9.0×10^{-07})	
rs288326	*FRZB*	T	Cases (n = 451) with incident RHOA during follow-up (mean 8.0 ± 0.4 years). Controls (n = 601)	HSM 2 (proximal femur SSM - smaller femoral head, steeper FN angle and narrower FN)	Beta -0.21 (0.019)	570 female cases with RHOA (of those 130 had femoral osteophyte) and 4,136 female controls	OR 3.18 (0.01) in patients with TT genotype and osteophytosis	(50, 72)
rs7775	*FRZB*	G		HSM 2 (proximal femur SSM - smaller femoral head, steeper FN angle and narrower FN)	Beta −0.23 (0.019)	570 female cases with RHOA (of those 326 had JSN) and 4,136 female controls	Frequency of the G allele was 0.11 in subjects with severe JSN ($P = 0.04$ versus controls)	(50, 72)

rs143384	*GDF5*	A	1,129 cases and 4,652 UKHLS controls	idiopathic DDH diagnosed in childhood	OR 1.44 (3.55×10^{-22})	Chinese and Japanese hip OA cases (N=1,000) and controls (N=984)	OR** 1.79 (p 3.1 $x10^{-11}$)	(47) (73)